the mammal, whereby the composition treats the tissue degenerative condition in the mammal, the composition comprising:

a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor selected from the group consisting of hormones, cytokines, peptides and growth factors, said factor being at a concentration effective to synergistically stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier;

wherein the MPSF is selected from the group consisting of IGF-I, hydrocortisone, insulin, and parathyroid hormone.

REMARKS

Applicants have canceled claims 93, 94, 100 and 101 without prejudice. As such, claims 69-88, 90, 91, 95-99 and 102-105 are pending in this application. Of these, claims 69, 74, 76 and 77 have been amended to promote clarity and to further define the scope of the invention.

Amendment 1

Applicants have further amended claims 69, 74, 76, and 77 to clarify that the morphogenic protein stimulatory factor be present at a concentration effective to "synergistically" stimulate the tissue inductive abilities of the morphogenic protein.

Support for this amendment is found in the alkaline phosphatase ("AP") assay results shown in Figures 1-10 and discussed at pp. 34-35 and 37 of the specification. The alkaline assay method is described at p. 34, lines 12-18:

> First, a MPSF is identified by picking one or more concentrations of a MPSF and testing them alone or in the presence of a morphogenic protein (**Examples 3 and 4**). Second, the amount of MPSF required to achieve optimal, preferably synergistic, tissue induction in concert with the morphogenic protein is determined by generating a dose response curve (**Example 3**). (boldface original; underscore added)

The results of the AP assays demonstrate that when present at certain concentrations, IGF-I, hydrocortisone, insulin, and parathyroid hormone are capable of synergistically stimulating the tissue inductive activity of a morphogenic protein (see also discussions below). As emphasized during the 1/25/02 interview by the undersigned, the novelty of the present invention lies in the unpredicted discovery that certain MPSFs induce a synergistic effect on the tissue-inductive activity of the BMPs.

Amendment 2

Applicants have also amended claims 69, 74, 76 and 77 to specify that the MPSF is one of "IGF-I, hydrocortisone, insulin, and parathyroid hormone." Support for this amendment appears in claim 87 as originally filed and in the specification, e.g., in Figs. 1-5, 7-9, and in Examples 3-5 and 7-13 (pp. 71-77 and 85-95).

Applicants respectfully request reconsideration of the pending claims in light of the above amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, 1st ¶

Claims 69-71, 74-80, 83-87, 90, 91, and 102-105 stand rejected for alleged lack of enablement. Specifically, the Examiner states that the specification does not reasonably provide enablement for a method of inducing formation, repair or integration of any and all tissues other than bone, ligament and tendon.[2] More particularly, the Examiner states that Example 13 does not demonstrate nerve regeneration, and that nerve cells cannot be replaced if lost. Office Action, pp. 2-3. Applicants respectfully traverse this rejection.

Numerous prior art studies have shown that neurons can be regenerated if damaged. In fact, Example 13 of the specification describes a method of determining the regeneration of damaged neurons. This method is similarly described in the cited prior art reference Wang (WO 95/05846).

During the 1/25/02 interview, the undersigned presented and discussed some of the additional pre-filing references that demonstrate the ability of neurons to regenerate if damaged. These references were Lein, Derby and Lundborg.[3] Lein shows that OP-1 can not only promote dendritic regeneration of mature neurons, but also induce dendritic growth of naive neurons. Derby demonstrates that the rat sciatic nerve can be regenerated when

2 During the 1/25/02 interview, the Examiner again acknowledged that the specification is enabling for bone, ligament and tendon.

3 Lein et al., Neuron 15:597-605 (September 1995) (Exhibit 1). This reference also describes that BMP/OP family members are important in neural development. For instance, OP-1, BMP-2, BMP-3, BMP-4, and BMP-5 are detected in at least one region of the brain, and BMP6 is expressed in most structures of the embryonic peripheral nervous system. Derby et al., Experimental Neurology 119:176-191 (1993) (Exhibit 2). Lundborg et al., J. Hand Surgery 7:580-587 (1982) (Exhibit 3).

damaged, and such a regeneration model can be used to monitor the effects of neutral trophic factors such as NGF. Lunborg similarly observes anatomic and functional regeneration of a transected sciatic nerve following regrowth from its proximal stump. In sum, the prior art demonstrates that neural regeneration does occur in adults. And applicants discovered and now claim that the combined use of neural trophic morphogens with certain MPSFs promotes that regeneration.

Like bone, tendon and ligament regeneration, the promotion of neuron regeneration is only one of the many embodiments of the claimed invention. Applicants' invention can be used to enhance the tissue inductive activity of morphonenic proteins that act on other tissues. During the 1/25/02 interview, the Examiner suggested that additional pre-filing references which demonstrate the diverse tissue specificity of BMPs would support applicants' position on the enablement issue.

Applicants hereby submit nine such references – Wang, Katagiri, Yamaguchi, Lyons, Ozkaynak, Jones, Maeno, King, and Schluesener.[4] These references collectively describe that

4 Wang et al., Growth Factors 9:57-71 (1993) (Exhibit 4). Katagiri et al., Journal of Cell Biology 127:1755-1766 (1994) (Exhibit 5). Yamaguchi et al., Journal of Cell Biology 113(3):681-687 (1991) (Exhibit 6). Lyons et al., Development 109:833-844 (1990) (Exhibit 7). Ozkaynak et al., Journal of Cell Biology 267(35):25220-25227 (1992) (Exhibit 8). Jones et al., Development 111(2):531-542 (1991) (Exhibit 9). Maeno et al., PNAS 91:10260-10264 (1994) (Exhibit 10). King et al., Developmental Biology 166:112-122 (1994) (Exhibit 11). Schluesener et al., Atherosclerosis 113:153-156 (1995) (Exhibit 12).

•BMP-2 exhibit effects on adipocytes (Wang), muscle cells (Katagiri and Yamaguchi), chondrocytes (Wang and Lyons), limb buds (Lyons), hair/whisker follicles (Lyons), heart cells (Lyons), and tooth buds (Lyons);

•BMP-3 plays a vital role in the liver and lung (Ozkaynak);

•BMP-4 exhibits effects on the liver and lung (Ozkaynak), hair/whisker follicles (Jones), heart (Jones), limb buds (Jones), pituitary gland (Jones), gut (Jones) and on erythropoiesis (Maeno);

•BMP-5 exerts effects on the liver, ureter, bladder and intestines (King); and

•BMP-6/Vgr-1 displays effects on the liver and lung (Ozkaynak), smooth muscle cells (Schluesener) and epithelial cells (Schluesener).

Thus, in light of the art at the time of the filing, the present specification clearly provides adequate enablement for using the claimed methods in tissues other than bone, ligament, tendon and neuron. All a skilled artisan needs to do is to use the recited MPSF with any of the numerous BMPs with known inductive activity in a tissue, to enhance that BMP's inductive activity in that tissue.[5]

Rejection Under 35 U.S.C. § 112, 2nd ¶

Claims 77-80, 83-87, 91, and 105 stand rejected as allegedly indefinite. Office Action, p. 3. Specifically, the Examiner contends the claims are allegedly indefinite

5 Applicants also note that an applicant need not demonstrate the operativeness of all species in the genus claim. MPEP § 2164.03.

because they "lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved" (p. 3, lines 4-5).

As discussed during the 1/25/02 interview, the Examiner and his supervisor both agreed that the term "treats" does in fact recite the result to be achieved and that no amendments would be necessary.

Rejection Under 35 U.S.C. § 102(b)

Claims 69-71, 77-80, and 83-87 stand rejected as allegedly anticipated by Wang (U.S. Patent 5,166,058; herein "the Wang patent" to distinguish from the Wang journal article attached as Exhibit 4). Applicants argued in the previous Response that this patent does not teach the use of IGF-I at a concentration effective to stimulate BMP-2 activity. In reply, the Examiner asserts that "all that the claims require is a morphogen and IGF-I, which is what Wang teaches" (Office Action, p. 3, lines 12-13). Moreover, the Examiner states that the features on which applicants rely upon (i.e., stimulate BMP-2 or OP-1 activity, simulation of AP activity) are not recited in the rejected claims. Office Action, p. 3-4. Applicants respectfully traverse this rejection.

Contrary to the Examiner's assertions, the rejected claims do recite specifically that the MPSF must be at a concentration "effective to stimulate" the tissue inductive activity of the morphogen. Nonetheless, in the sole interest of moving this case toward allowance, applicants have proposed herein to amend the base claims to particularly point out that the MPSF must be present at an effective concentration to "synergistically"

stimulate the tissue inductive activity of the morphogenic protein. Nowhere in the Wang patent is this feature even mentioned.

The Examiner also states that TGF-β and BMP synergize to promote the formation of endochondral bone *in vivo* based on Ogawa (Ogawa et al., Journal of Biological Chemistry 267(20):14233-14237). Ogawa is irrelevant. The rejected claims do not include TGF-β as an MPSF.

Thus, none of the rejected claims are anticipated by Wang and applicants request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102(e)

Claims 77 and 85 stand rejected as allegedly anticipated by Kuberasampath (U.S. Patent 5,674,844). In response to applicants' previous arguments, the Examiner asserts that the features upon which the applicants relies (i.e., synergism) are not recited in the rejected claims. Office Action, p. 4.

As discussed above, the proposed amendments requires that the MPSF be present at a concentration effective to "synergistically" stimulate the tissue inductive activity of an MP. This important feature is not taught in Kuberasampath.

The Examiner contends that the term "beneficial" used in Kuberasampath and "MPSF" are indistinguishable. It is not so. Kuberasampath's "beneficial" is ambiguous and not clearly defined. The reference merely says that factors known to have a "beneficial effect on bone modeling" can be co-administered with an MP. Col. 4, lines 58-65. Many factors may be "beneficial on bone modeling," but not all of them can exert a synergistic effect

on a morphogenic protein itself. For instance, these factors may have only algebraically additive, rather than synergistic, effects on a BMP. In short, Kuberasampath does not contain an inkling of the notion that IGF-I, hydrocortisone, insulin, and parathyroid hormone can synergistically stimulate the activity of an MP.

Furthermore, the Examiner points to the effect of TGF-β on BMP mentioned in Ogawa. However, as discussed above, Ogawa is irrelevant.

Rejections Under 35 U.S.C. § 103(a)

I

Claims 74 and 75 stand rejected as allegedly obvious over the Wang patent in view of Kuberasampath (U.S. Patent 4,968,590). The Examiner asserts that no difference is seen between "agents beneficial to the treatment of the bone defect," i.e., IGF-I and a "MPSF." Office Action, pp. 4-5. Applicants respectfully traverse.

As discussed above, the Wang patent does not teach synergism, a claim element made even more express by the proposed amendment. Kuberasampath does not remedy this deficiency by using the vague term "beneficial." Thus, the instant rejection should be withdrawn.

II

Claim 76 stands rejected as allegedly obvious over Rueger (U.S. Patent 5,344,654) in view of the Wang patent. Office Action, p. 5. Again, the Examiner asserts that there is no different between "agents beneficial to the treatment of the bone defects", i.e., IGF-I and a "MPSF". Applicants respectfully traverse this rejection.

As already discussed above, Wang does not teach synergism, a claim element now recited expressly in claim 76. Rueger, which is cited for teaching prosthetic devices coated with substantially pure osteogenic protein, does not remedy this deficiency. Thus, this rejection should be withdrawn.

III

Claims 77, 90 and 91 stand rejected as allegedly obvious over Kuberasampath (U.S. Patent 5,674,844) as applied to claim 77 above and further in view of Hock (Hock et al., *Endocrinology* 122:254-60 (1988)) and further in view of Baylink or the Wang patent. According to the Examiner, no difference is seen between administering OP-1 together with other "cofactors" known to have a beneficial effect on bone remodeling such as IGF-I and administering OP-1 with an "MPSF." Office Action, p. 5, lines 10-12. Applicants respectfully traverse.

As discussed above, the proposed amendments recites synergism between MPSF and MP. This characteristic of the MPSF differs from cofactors which exhibit general beneficial effects on bone remodeling.

Further, the Examiner himself seems to acknowledge that the synergism between OP-1 and IGF-I is "surprisingly." Office Action, p. 5, line 15. Indeed, as discussed in applicants' previous Response and during the 1/25/02 interview, applicants discovered that unlike IGF-I, IGF-II cannot stimulate OP-1-induced osteogenic induction. Fig. 11 and p. 7, lines 16-23. This discovery demonstrates that one of ordinary skill in the art would not have any reasonable expectation that combinations of BMPs with the four MPSFs recited in the

claims result in synergism. None of the other cited references, Hock, Baylink or Wang, remedy this deficiency.

New Rejections Under 35 U.S.C. §103(a)

I

Claims 69 and 102 stand newly rejected as allegedly as obvious over the Wang patent as applied to claim 69 above and further in view of Kuberasampath (WO 91/18558). According to the Examiner, Wang teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I and is silent with respect to the carrier comprising heparin. The Examiner asserts that Kuberasampath teaches a device comprising a carrier comprising heparin. On this basis, the Examiner states that it would have been obvious to combine the two references to arrive at the claimed invention. Applicants respectfully traverse.

As already discussed above, Wang does not teach or suggest synergism, a key feature of the claimed invention. This Kuberasampath does not remedy this deficiency. Thus, the Examiner has not established a *prima facie* case of obviousness against claims 69 and 102.

II

Claims 77 and 105 stand rejected as allegedly as obvious over Kuberasampath (US Patent 5,674,844 - e7) as applied to claim 77 above and further in view of Kuberasampath (WO 91/18558 - n11). According to the Examiner, Kuberasampath (e7) teaches a method of administering a composition comprising a carrier, morphogen and IGF-I.

Kuberasampath (n11) teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, Kuberasampath (e7) does not teach that the MPSF must be at a concentration effective to synergistically stimulate the tissue inductive activity of an MP, as proposed in the 37 C.F.R. 1.116 amendments. Kuberasampath (n11), which is cited for teaching a device comprising a carrier comprising heparin, does not remedy this deficiency. Thus, the instant rejection should be withdrawn.

III

Claims 74 and 103 stand rejected as allegedly as obvious over the Wang patent and Kuberasampath (c7) as applied to claim 74 above and further in view of Kuberasampath (WO 91/18558).

According to the Examiner, Wang in view of Kuberasampath (c7) teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I.. Kuberasampath (n11) teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, Wang does not teach the use of a composition containing an MP and an MPSF that is at a concentration effective to synergistically stimulate the tissue inductive activity of the MP, as proposed in the 37 C.F.R. 1.116 amendments. Neither Kuberasampath (c7) or Kuberasampath (n11) remedy this deficiency. Thus, the

Examiner has not established a *prima facie* case of obviousness since the combination of these references do not teach synergism, which is now a claim element as proposed in the 37 C.F.R. 1.116 amendments.

IV

Claims76 and 104 stand rejected as allegedly as obvious over Rueger in view of Wang as applied to claim 76 above and further in view of Kuberasampath (WO 91/18558). According to the Examiner, Rueger in view of Wang teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I.. Kuberasampath (n11) teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, Rueger does not teach synergism, as recited in the proposed amendments. Neither Wang or Kuberasampath (n11) remedies this deficiency.

V

Claims 77 and 105 stand rejected as allegedly as obvious over Kuberasampath (e7) as applied to claim 77 above and further in view of Hock and further in view of Baylink or Wang and further in view of Kuberasampath (WO 91/18558). According to the Examiner, Kuberasampath (e7) as applied to claim 77 above and further in view of Hock and further in view of Baylink or Wang teaches a method of administering a composition comprising a carrier, a morphogen and IGF-I. Kuberasampath (n11) teaches a device comprising a carrier comprising heparin. The Examiner asserts that one of ordinary

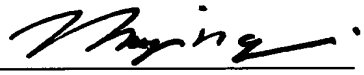
skill in the art would be motivated to combine these teachings with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, Kuberasampath (e7) does not teach that the MPSF must be at a concentration effective to synergistically stimulate the tissue inductive activity of an MP, as recited in the proposed 37 C.F.R. 1.116 amendments. Hock, Baylink or Wang, either alone or in combination, do not remedy this deficiency.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims. Applicants' undersigned agent welcomes the Examiner to telephone her to discuss this Response should such need arise.

Respectfully submitted,



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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: COMMISSIONER FOR PATENTS P.O. Box 2327 ARLINGTON, VA 22202 on

April 9, 2002

Lillian Garcia



Signature of Person Signing

Appendix of Amended Claims

69. (Three Times Amended) A method for inducing local tissue formation from a progenitor cell in a mammal comprising the step of implanting in the mammal a morphogenic device at a locus accessible to at least one progenitor cell of the mammal, whereby the morphogenic device induces local tissue formation from the progenitor cell in the mammal, the morphogenic device comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of hormones, cytokines, peptides and growth factors disposed in the carrier, the stimulatory factor being at a concentration effective to **synergistically** stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell,

wherein the MPSF is selected from the group consisting of IGF-I, [growth hormone,] hydrocortisone, insulin, **and** parathyroid hormone [and progesterone].

74. (Three Times Amended) A method of accelerating allograft repair and incorporation in a mammal, comprising the step of implanting at a locus in need of replacement bone a matrix-comprising device, whereby the device accelerates allograft repair and incorporation in the mammal, the device comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of hormones, cytokines, peptides and growth factors disposed in the carrier, the stimulatory factor being at a concentration effective to **synergistically** stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell,

wherein the MPSF is selected from the group consisting of IGF-I, [growth hormone,] hydrocortisone, insulin, **and** parathyroid hormone [and progesterone].

76. (Three Times Amended) A method of promoting in vivo integration into a target tissue of a mammal an implantable prosthetic device, the method comprising the steps of:

a) providing on a surface of the prosthetic device an osteogenic composition, and

b) implanting the device in a mammal at a locus where the target tissue and the surface of the prosthetic device are maintained at least partially in contact for a time sufficient to permit enhanced tissue growth between the target tissue and the device,

wherein the osteogenic composition comprises (1) an morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and (2) a morphogenic protein stimulatory factor (MPSF) at a concentration effective to **synergistically**

stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell, said morphogenic protein and MPSF disposed on the surface region in an amount sufficient to promote from a progenitor cell enhanced tissue growth between the target tissue and the device;

wherein the MPSF is selected from the group consisting of IGF-I, [growth hormone,] hydrocortisone, insulin, **and** parathyroid hormone [and progesterone].

77. (Three Times Amended) A method of treating a tissue degenerative condition in a mammal comprising the step of administering a pharmaceutical composition to the mammal, whereby the composition treats the tissue degenerative condition in the mammal, the composition comprising:

a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor selected from the group consisting of hormones, cytokines, peptides and growth factors, said factor being at a concentration effective to **synergistically** stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier;

wherein the MPSF is selected from the group consisting of IGF-I, [growth hormone,] hydrocortisone, insulin, **and** parathyroid hormone [and progesterone].